Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the
Peripheral and Central Nervous System Drugs Advisory Committee Meeting
May 24, 2012

Location: The FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland

Topic: The committee discussed new drug application (NDA) 202737, for tafamidis meglumine capsules, proposed trade name VYNDAQEL, submitted by FoldRx Pharmaceuticals, Inc., a subsidiary of Pfizer, Inc. The proposed indication is for the treatment of transthyretin (TTR) familial amyloid polyneuropathy.

These summary minutes for the May 24, 2012, meeting of the Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration were approved on July 3, 2012.

I certify that I attended the May 24, 2012, meeting of the Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____/s/_____
Glendolynn S. Johnson, Pharm.D.
Designated Federal Officer, PCNS

_____/s/_____
Nathan B. Fountain, M.D.
Acting Chair, PCNS

Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting
May 24, 2012

The following is the final report of the Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) meeting held on May 24, 2012. A verbatim transcript will be available in approximately six weeks, sent to the Division of Neurology Products and posted on the FDA website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/ucm298454.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on May 24, 2012 at the FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the background materials from the FDA and Pfizer, Inc. The meeting was called to order by Nathan Fountain, M.D. (Acting Chair); the conflict of interest statement was read into the record by Glendolynn S. Johnson, Pharm.D. (Designated Federal Officer). There were approximately 120 people in attendance. There were fifteen Open Public Hearing speakers.

Issue: The committee discussed new drug application (NDA) 202737, for tafamidis meglumine capsules, proposed trade name VYNDAQEL, submitted by FoldRx Pharmaceuticals, Inc., a subsidiary of Pfizer, Inc. The proposed indication is for the treatment of transthyretin (TTR) familial amyloid polyneuropathy.

Attendance:
PCNS Members Present (Voting): Jeffrey A. Cohen, M.D.; Nathan B. Fountain, M.D. (Acting Chair); Samuel A. Frank, M.D. (Consumer Representative); Ellen J. Marder, M.D.

PCNS Members Not Present (Voting): Pooja Khatri, M.D.; Jason W. Todd, M.D.

PCNS Member Present (Non-Voting): Lynn Kramer, M.D., FAAN (Industry Representative)

Temporary Members (Voting): Emilia Bagiella, Ph.D.; Vinay Chaudhry, M.D.; Robert R. Clancy, M.D.; Erik R. Ensrud, M.D.; Clifton L. Gooch, M.D., FAAN; Tiffany House (Patient Rep); Eric L. Logigian, M.D.; Michelle Mielke, Ph.D.; Anne L. Oaklander, M.D., Ph.D.; David C. Preston, M.D.; Paul B. Rosenberg, M.D.; Jeremy Shefner, M.D., Ph.D.; Ashok Verma, M.D., D.M., M.B.A.

FDA Participants (**Non-Voting):** Ellis Unger, M.D.; Russell Katz, M.D.; Ronald Farkas, M.D., Ph.D.; Devanand Jillapalli, M.D.; Julia Luan, Ph.D.

Designated Federal Officer (Non-Voting): Glendolynn S. Johnson, Pharm.D.

Open Public Hearing Speakers: Diane Edquist Dorman (National Organization for Rare Disorders); Patricia Gibson (Amyloidosis Support Group); Michael Clark; Jorja J. Kline (Hagerstown Chapter of the Amyloidosis Support Group); Ellen Cameron; Geri O'Brien; Robert (Bobby) O'Brien; Arnold Goldstein; Kevin Mui; Dean Suhr (Patient Advocacy Advisory Board, RARE Project); Martin McGarry; Natacha T. Pires, M.B.B.S. (The Neuropathy Association); (b) (6) Kristin Prete; Darren K. Robinson

The agenda proceeded as follows:

Call to Order and Introduction of Committee	**Nathan B. Fountain, M.D.** Acting Chair, PCNS
Conflict of Interest Statement	**Glendolynn S. Johnson, Pharm.D.** Designated Federal Officer, PCNS
FDA Introductory Remarks	**Russell Katz, M.D.** Director Division of Neurology Products (DNP) Office of Drug Evaluation I (ODE I) Office of New Drugs (OND), CDER, FDA
SPONSOR PRESENTATION	**Pfizer, Inc.**
Introduction	**Clare Kahn** Vice President Worldwide Regulatory Strategy Specialty Care, Pfizer
Disease Background and Treatment Paradigm	**Steven R. Zeldenrust, M.D., Ph.D.** Assistant Professor of Medicine Mayo Clinic Rochester, MN
Tafamidis MOA and Clinical Pharmacology	**Jeffery Kelly, Ph.D.** Lita Annenberg Hazen Professor of Chemistry Scripps Research Institute La Jolla, CA
Clinical Endpoints in TTR-FAP	**Roy Freeman, M.D.** Professor of Neurology Director, Center for Autonomic and Peripheral Nerve Disorders Harvard Medical School Boston, MA
Tafamidis Efficacy and Safety	**Donna Grogan, M.D.**

	Medical Consultant Former Chief Medical Officer, FoldRx (a wholly owned subsidiary of Pfizer, Inc.)
TTR-FAP Clinical Perspective	**Teresa Coelho, M.D.** Largo Prof. Abel Salazar Hospital Geral de Santo Antonio Porto, Portugal
Tafamidis Benefit:Risk Assessment	**Ilise Lombardo, M.D.** Senior Director, Medicines Development Group Pfizer, Inc.

Clarifying Questions

BREAK

FDA PRESENTATION

Tafamidis in Transthyretin Amyloid Polyneuropathy	**Ronald Farkas, M.D., Ph.D.** Clinical Team Leader, DNP ODE-I, OND, CDER, FDA

Clarifying Questions

LUNCH

Open Public Hearing Session

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION**: Please discuss the strengths and weaknesses of study 005, including the effects of the following factors on its ability to provide substantial evidence of effectiveness. Please discuss how regulatory flexibility might be applied with regard to these factors.

    a. p-value for the pre-specified co-primary endpoint
    b. Nominal p-values for the individual components of the co-primary endpoint
    c. p-value for efficacy-evaluable population
    d. Lack of control for multiple testing in the analyses of secondary endpoints
    e. Results of secondary endpoints

f. Baseline imbalances

g. Disproportionate support of efficacy from site 1 in Portugal, with little to no efficacy support from combination of remaining sites

Committee Discussion*:*

1a. The committee agreed that the p-value for the pre-specificied co-primary endpoint was not statistically significant.

1b. The committee agreed that the nominal p-values for the individual components of the co-primary endpoint were not statistically significant.

1c. The committee noted that normally the primary efficacy analysis should be based on intent to treat (ITT); however,some committee members suggested primary efficacy might be based on the efficacy evaluable population for this unusual study population.

1d. The committee agreed that there was a lack of control for multiple testing in the analyses of secondary endpoints.

1e. The committee believed the data was not compelling enough to draw any strong conclusions from the results of the secondary endpoints.

1f. The committee believed there were clinically meaningful baseline imbalances.

1g. The committee believed that efficacy evidence was weakened by the dominant effect of a single site in Portugal.

Please see the transcript for details of the Committee discussion.

2. For approval based on a single study plus confirmatory evidence, the study is expected to be particularly robust. Note, however, that not all characteristics that might make a study particularly robust need to be present.

   a. **VOTE**: In the context of the above discussion, are the findings of study 005 sufficiently robust to provide substantial evidence of efficacy similar to that usually provided by two supportive studies for a ***clinical*** endpoint?

      YES: 4 NO: 13 ABSTAIN: 0

      i. If you voted "Yes" in question #2a, please discuss how.

      Committee Discussion: *The majority of the committee agreed that the findings of study 005 were not sufficiently robust to provide substantial evidence of efficacy similar to that usually provided by two studies each positive for a clinical endpoint. The committee members who voted "YES" noted that although the efficacy evidence was not robust there was some evidence of efficacy shown for such a short period.*

b. **VOTE**: In the context of the above discussion, are the findings of study 005 sufficiently robust to provide substantial evidence of efficacy similar to that usually provided by two supportive studies for a ***biomarker*** endpoint that is reasonably likely to predict a clinical benefit?

YES: 13 NO: 4 ABSTAIN: 0

i. If you voted "Yes" in question #2b, please discuss how.

Committee Discussion: *The majority of the committee agreed that the findings of study 005 were sufficiently robust to provide substantial evidence of efficacy similar to that usually provided by two supportive studies for a biomarker endpoint that is reasonably likely to predict a clinical benefit. The committee members who voted "YES" stated the following as specific reasons for their vote: the small fiber composite endpoint, TTR stabilization, and the muscle strength component of the neuropathy impairment score in the lower limbs (NIS-LL).). Those members who voted "NO" indicated that they were not convinced that TTR stabilization equated to clinical benefit, or that substantial evidence had been presented for small fiber or strength endpoints.*

Please see the transcript for details of the Committee discussion.

3. **VOTE**: If the answer to Question #2a and #2b is "No", is study 005 'positive' in the sense of providing evidence of similar robustness to that provided by a single study with primary endpoint with a p-value less than or equal to 0.05?

Based on the discussions that transpired, the committee did not address question #3.

4. **DISCUSSION**: Study 006 does not have the characteristics of an adequate and well-controlled trial, but may provide supportive evidence of effectiveness for tafamidis. Please discuss the strengths and weakness of study 006 as a source of supportive evidence, including the effect of the following factors:

a. Analysis of many endpoints without control for multiple testing
b. Dependence on differences between arms present at the end of study 005
c. Imbalances present in study 005
d. Open-label design (including, for example, risk of unblinding and bias from non-random dropouts)

Based on the discussions that transpired, the committee did not address question #4.

5. **VOTE**: Does study 006 provide supportive evidence of efficacy?
a. If you voted "Yes" in question #5, please discuss how.

Based on the discussions that transpired, the committee did not address question #5.

6. **DISCUSSION**: Please discuss if there is other evidence that is particularly persuasive of efficacy. If so, what?

Committee Discussion: *The committee agreed that TTR testing was particularly persuasive of efficacy. Please see the transcript for details of the Committee discussion.*

7. **DISCUSSION**: Please discuss if there are any particular concerns about safety.

Committee Discussion: *The committee did not have any particular concerns regarding safety. However, since urinary tract infections (UTIs) were listed as a prominent adverse event, the panel members discussed if the UTIs were a result of the drug product or unrelated factors , such as patients self-catherization. The committee agreed that conclusive evidence was not available. Please see the transcript for details of the Committee discussion.*

The meeting was adjourned at approximately 4:30 p.m.